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BY

F. PARKES WEBER, M.A., M.D., F.R.C.P.,

SENIOR PHYSICIAN TO THE GERMAN HOSPITAL, LONDON, AND PHYSICIAN TO THE MOUNT VERNON HOSPITAL FOR DISEASES OF THE CHEST, HAMPSTEAD, LONDON, ENGLAND.

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ACQUIRED CHRONIC ACHOLURIC JAUNDICE, WITH A BLOOD PICTURE AT ONE TIME RESEMBLING THAT OF PERNICIOUS ANEMIA.

By F. Parkes Weber, M.A., M.D., F.R.C.P.,

SENIOR PHYSICIAN TO THE GERMAN HOSPITAL, LONDON, AND PHYSICIAN TO THE MOUNT VERNON HOSPITAL FOR DISEASES OF THE CHEST, HAMPSTEAD, LONDON, ENGLAND.

The patient, Mrs. L. P., now aged thirty-eight years, was admitted under my care at the German Hospital in January, 1908, with blood changes charactcristic of pernicious anemia, and on April 13, 1908, she was shown at the Medical Society of London as a "Case of Enlargement of the Spleen and Liver with Pernicious Anemia." She was again shown at the same socicty on February 8, 1909.

Up to the time of admission the history was that the patient had previously been healthy. About three years back she began to get paler, and about a year later she had an attack of deep jaundice (with pains in the right side), which was followed by dropsy. After that she gradually bccame weaker and paler and short of breath on exertion. Menstruation became scanty, and for a timc there was complete amenorrhœa. She suffered from rccurrent epistaxis. She was troubled with coldness and numbness of the hands and feet; sometimes she had a sensation of pins and needles in the fingers, which would often "go blue."

In regard to the family history it was to be noted that her mothcr had died of livcr disease, aged fifty-two years. The patient herself was a widow, who had been married twice. By hcr first husband she had two children, the first one born dead, the second one still living and healthy. By her second husband (who was addictcd to alcohol) she had no children.

After admission to the hospital the condition notcd was the following: The skin and conjunctivæ were yellowish. There was no pruritus or xanthoma. The legs were œdematous. The heart seemcd slightly dilated, and there was a faint systolic murmur, apparently not due to valvular disease. Thc liver and spleen wcre both evenly enlarged. The liver cxtcnded two or thrce finger brcadths bclow the ribs, and the splecn, which was hard, reachcd almost to the anterior superior iliac spine. Thc condition of the patient's mouth was not bad, though shc had lost many of her teeth. Occasionally there was slight bleeding from the gums.

Attacks of epistaxis were frequent. Ophthalmoscopic examination (Dr. C. Markus) showed numerous bright red, round, retinal hemorrhages in both eyes, chiefly in the upper halves of the fundi. The urine, of specific gravity 1013, contained albumin (1 per mille by Esbach's tube on admission), but no tube-casts. A later note of the urine stated it to be of specific gravity about 1015, of deep orange color, free from albumin and sugar, and giving no Gmelin's reaction for bile pigment, but containing excess of urobilin. The feces were never acholic.

Examination of the blood on January 31, 1908, gave the following result: Hemoglobin (by Haldane's method), 18 per cent.; red corpuscles, 900,000 in the cubic millimetre; white corpuscles, 6000; color index, 1. From a preparation of the same date Dr. A. E. Boycott made the following differential count of 500 white cells: Lymphocytes, 45.6 per cent; intermediates, 4.8; large hyalines, 2.4; neutrophile polymorphonuclears, 46; eosinophiles, 0.8; mast-cells, 0.4. During the count of 500 white cells he saw no ordinary normoblasts, but eight typical megaloblasts (that is to say, megaloblasts with cytoplasm staining as in the typical megaloblasts of pernicious anemia) and 16 smaller nucleated red cells resembling the typical megabololblats except in regard to their relatively small size. There were a few polychromatophilic red cells and many punctate basophilic red cells. Poikilocytosis (as to shape and size of the red cells) was characteristic for pernicious anemia. No myelocytes were seen. An examination (May, 1908) of the contents of the stomach one-hour after a test breakfast consisting of dry bread and tea showed the absence of free hydrochloric acid.

The treatment in the hospital consisted chiefly of rest (at first rest in bed), subcutaneous injections of the arsenic preparation, known as atoxyl, chalybeate medicines by the mouth, and acid glycerin of pepsin after meals. The amount of atoxyl injected was usually 0.1 gram (that is to say, 1 c.c. of a 10 per cent. solution) twice weekly. Calcium lactate was occasionally given on account of urticaria and subcutaneous hemorrhages. For about a week in September inunction of the splenic region with an ointment of the biniodide of mercury was tried, but with no definite result. The atoxyl treatment was commenced very soon after the patient's admission in January, 1908. It was continued with intervals till July 21, 1908, and then discontinued.

The patient has been over a year in the hospital. Progress was for a long time very slow and rather unsatisfactory, but decided improvement was observed in November, 1908, and has continued since then. The patient now feels and looks almost quite well. She has long been allowed to get up. She is free from jaundice, fever, and œdema and has gained considerably in body weight (133½ pounds in February, 1909, as compared with 118¼ pounds in February, 1908). The blood shows only slight anemia. The heart is not dilated, and

shows nothing abnormal except a very slight systolic murmur best heard in the pulmonary area. The pulse frequency is 82 to 96 in the minute. The brachial systolic blood pressure is 100 mm. Hg. The spleen can only just be felt. The edge of the liver cannot be felt, though the organ is still probably somewhat enlarged. The retinæ are free from hemorrhages, but the patient continues to suffer from attacks of epistaxis at short intervals. Menstruation has recently recommenced, after a prolonged period of amenorrhœa. The stomach contents after a test meal show the presence of free hydrochloric acid. There is no excess of urobilin in the urine and the blood serum (kindly examined by Dr. Leonard Dudgeon on November 25, 1908) is free from bile pigment.

Several features of the patients' illness require special mention and consideration.

Abdominal Pain. At various times the patient has complained of pain or tenderness in the upper part of the abdomen, sometimes in the region of the liver, sometimes associated with fever. An attack about the middle of August, 1908, was associated with vomiting and temporary increase of the icteric tinge; a short attack in December was accompanied by a sudden rise of temperature to 103° F.

Jaundice. While under observation the patient was never deeply jaundiced, but the conjunctivæ for a long while were distinctly yellow. With the improvement in the general condition in November the jaundice entirely disappeared, and has not reappeared since. With a single doubtful exception (during a temporary exacerbation of the jaundice), bile pigment was never present in the urine; the feces were never acholic.

Temperature. At first there were recurrent periods of moderate fever, but since September there has been hardly any. The last occasion on which any fever occurred was on December 13, when a temperature of 103° F. was noted in association with abdominal pain.

Retinal and Other Hemorrhages. The retinal hemorrhages noted by Dr. C. Markus were peripheral in distribution, and chiefly in the right eye. They temporarily disappeared in the early part of April, 1908, but were noted again at the end of the month and in August and September. There are none to be seen at present. Recurrent attacks of epistaxis have been a feature throughout the illness. They still occur at short intervals, but for several months she has had no bleeding from the gums. In addition to these hemorrhages several bluish bruise-like subcutaneous hemorrhagic patches were observed during August and September, 1908. They were nearly all on the limbs. It is a question whether these various hemorrhages, as well as an urticarial tendency noted in February and March, 1908, might not be connected with diminished coagulability of the blood, or increased tendency to hemolysis (see later on).

Condition of the Blood. On May 19, 1908, the number of red cells in the cubic millimetre of blood had risen from 900,000 (on admission) to 2,000,000, and the hemoglobin from 18 per cent. to 35 per cent., but this improvement was hardly maintained. On July 4 the red cells were only 1,550,000, and the examination of blood films still showed the presence of typical megaloblasts. On August 15 another blood count was made. The red cells were then 1,300,000 and the white cells 8200 in the cubic millimetre. Dr. Boycott kindly forwarded the following differential count of 500 white cells: Lymphocytes, 51.2 per cent.; intermediates, 9.6; large hyalines, 1.2; neutrophile polymorphonuclears, 37.6; eosinophiles, 0.4; mast-cells, 0. He likewise reported that one neutrophile myelocyte and two nucleated red cells (small type with polychromatophilic cytoplasm) were found. The red cells showed moderate poikilocytosis and variation in size, but there were extremely few that were too big. The blood picture was certainly no longer that of pernicious anemia. By December 8 the number of red cells had risen to 3,277,000 in the cubic millimetre, and the hemoglobin was estimated by Haldane's method at 70 per cent.; nothing much abnormal could be made out by microscopic examination. On December 21 the red cells numbered 4,123,000, and the white cells 6250; hemoglobin, 74 per cent. Dr. Boycott, who again kindly examined blood films, found nothing abnormal in the red and white cells. His differential count of white cells then gave lymphocytes, 26.6 per cent.; intermediates, 2.2; large hyalines, 2; neutrophile polymorphonuclears, 68.4; eosinophiles, 0.8; mast-cells, 0.

It is interesting to note the increase in blood-viscosity accompanying the increase in the number of corpuscles. On February 23, doubtless by reason of the corpuscular deficiency, the viscosity was very low; by Determann's clinical viscosimeter at 20° C. it was found to be only 2.6 times that of water at the same temperature. Estimated in the same way, on January 20, 1909, it was found to be 4 times that of water.

Owing to the hemorrhagic tendency manifested in the patient, her blood coagulability was repeatedly estimated by Sir A. E. Wright's coagulometer. The coagulation time varied on different occasions between ten minutes and fifteen minutes twelve seconds.

As it was supposed that excessive hemolysis might be the cause of the patient's acholuric jaundice ("acquired hemolytic jaundice" of A. Chauffard, F. Widal, Abrami, Brulé, etc.), the resistance of the red cells to hemolysis was repeatedly tested by Ribierre's method.[1] It was found that hemolysis usually occurred when a few drops of the patient's blood diluted with normal salt solution were added to a solution of between 0.46 and 0.44 parts per cent. of sodium chloride

[1] I am greatly indebted to Dr. Chapuis, one of the house physicians at the hospital, for much assistance in the clinical examination of the case, especially in regard to the hemolysis examinations, and to Dr. Trendelenburg, who replaced Dr. Chapuis for a short time.

in distilled water. On one occasion it occurred still more readily (between 0.48 and 0.46), but lately the resistance of the red cells has apparently somewhat increased, for it now takes a solution of between 0.44 and 0.42 parts per cent. of sodium chloride in distilled water to produce hemolysis. The fragility, therefore, of the red cells, though rather high, appears not to be very greatly in excess of the normal. The hemolysis was not, however, examined by the method of adding the patient's red cells deprived of their plasma to the various solutions.

Dr. Leonard Dudgeon very kindly made some further investigations with the patient's blood on November 25, 1908, when her general condition was rapidly improving. From her blood he separated samples of her blood serum and of her red cells. He found that her serum had no hemolytic action on the red cells obtained from a normal (healthy) person or on her own red cells (that is, her serum possessed no autohemolytic action); neither did the blood serum from a normal person exert any hemolytic action on the patient's red cells. Furthermore, no hemagglutinative action was observed (by the methods employed by Dudgeon) on adding the patient's blood serum to a normal person's red cells, the patient's red cells to a normal person's serum, or the patient's serum to her own red cells.[2] No hemophagocytosis was observed.

On the whole, the present case seems to fit in best with the cases described by various authors on the Continent as examples of "Acquired Chronic Acholuric Jaundice with Splenomegaly and Anemia." The present case confirms Chauffard's opinion (as cited by Rolleston) that acquired cases of splenomegalic jaundice show more anemia and less jaundice than the congenital cases.[3] The remarkable feature of the case was the severity of the anemia which was at first accompanied by a myeloid (hemopoietic) reaction of the megaloblastic type, as in typical cases of pernicious anemia. It is not certain in the present case that the anemia was really hemolytic in origin, although the resistance of the patient's red blood cells to hemolysis was decidedly less than that noted in various healthy persons (controls) with whose blood hers was repeatedly compared.

Postmortem examinations have shown that some cases of acquired chronic acholuric jaundice are complicated by cholelithiasis. In the

[2] For Dr. Dudgeon's methods see his preliminary report "On the Presence of Hemagglutinins, Hemopsonins, and Hemolysins in the Blood Obtained from Infectious and Non-infectious Diseases in Man," Proceedings of the Royal Society, London, 1908, Series B, vol. lxxx, p. 531.

[3] I have, however, satisfied myself that patients with congenital splenomegalic acholuric jaundice may sometimes (for a time at least) completely lose their icteric tinge. In other words, the jaundice may disappear and leave a condition of splenomegalic anemia only. Moreover, in the same family one child may suffer from congenital splenomegalic acholuric jaundice, whilst another child may suffer from chronic splenomegalic anemia without any manifest jaundice, though the blood picture be the same in both children. Evidently, in such instances the splenomegalic anemia is the same disease, whether it be accompanied by visible jaundice or not.

present case, indeed, the abdominal pains gave rise to a suspicion of gallstone trouble, while the reeurrent attaeks of epistaxis suggested the association of hepatic cirrhosis. The possibility of cholelithiasis sceondary to ehronic infeetion of the bile passages with typhoid bacilli was likewise considered, but the patient says she has never had typhoid fever, and her feces have been bacteriologically examined for typhoid baeilli with a negative result; moreover, Widal's reaction was twice tried, and on both occasions the result was negative.

The great improvement that has taken plaee in the patient's condition is very satisfaetory, but this result cannot with certainty be attributed to the atoxyl treatment, as the period of the most decided improvement commeneed a considerable time after the atoxyl treatment had been eoneluded. The main improvement appeared almost sudden enough to be termed a "erisis," but it was not aceompanied by the blood changes (espeeially the large proportion of erythroblasts, some of them in stages of mitotic division) eharaeteristic of typieal "blood crises" in various forms of chronic anemia; that is to say, unless a true blood crisis of the kind commenced and ended during a specially long interval between two blood examinations.